REMARKS

I. The invention

The present invention relates to a tissue adhesive comprising fibrinogen and an elastase inhibitor, wherein the elastase inhibitor is capable of inhibiting fibrinolysis.

II. Status of the claims

Claims 29, 33, 36-42, 51, 54-60, and 70-73 are under examination. Claims 29 and 70 are amended. Claims 30, 31, 32, 34, 35, 43-50, 52, 53, and 61-69 are cancelled.

III. Rejection under 35 U.S.C. §103(a)

The Examiner rejected claims 29, 30, 33, 36-42, 51, 54-60, and 70-73 under 35 USC §103(a) as allegedly being obvious over U.S. Patent No. 5,418,221 (Hammarstrom) or U.S. Patent No. 5,631,011 (Wadstrom) in view of U.S. Patent No. 5,271,939 (Robertson) or WO 92/22309 (Mehta) and further in view of U.S. Patent No. (Akinson). Applicants respectfully traverse this rejection.

The Examiner states that one of skill in the art would have been motivated to combine the elements of the present invention, a fibrinogen adhesive and an elastase inhibitor, as each of these components are generally used in wound healing.

To establish a *prima facie* case of obviousness, three basic criteria must be met: first, the prior art references must teach or suggest all the claim limitations; second, there must be some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill in the art, to combine the limitations; third, there must be a reasonable expectation of success in combining the limitations. MPEP §2143. Furthermore, it is well recognized that an obviousness rejection requires a particularized teaching or suggestion to combine the elements to make the claimed invention. *See In re Mills,* 16 USPQ 2d 1430 (Fed. Cir. 1990); *see also In re Fritch*, 23 USPQ2d 1780 (Fed. Cir. 1992).

The claims as amended now recite a tissue adhesive comprising fibrinogen and a specific elastase inhibitor selected from the group consisting of eglin and α1-antiprotease. The present invention is a separately patentable combination of fibrinogen and either eglin and/or α1-antiprotease for a specific use in wound healing (as a tissue adhesive). The cited references in combination do not teach or disclose either eglin or α1-antiprotease as specifically useful in wound healing, much less as useful for tissue adhesion. The cited art therefore fails to motivate one of skill in the art by providing a particularized teaching or suggestion to combine the elements to make the claimed invention.

With respect to the fibrinogen-based tissue adhesives, Waldstrom discloses the use of such compositions generally for wound healing and other therapeutic uses, while Hammarstrom focuses on the use of such compositions for wound healing in dental surgeries. Waldstrom and Hammarstrom do not teach the use of elastase inhibitors for tissue adhesives.

With respect to elastase inhibitors, Robertson generally discloses the use of elastase inhibitors for treatment and prevention of corneal scar formation during laser surgery. These elastase inhibitors were used as epithelial cell health promoters known to contribute to the overall health of epithelial cells of the cornea (column 11 lines 37-44 and column 12 lines 3-15). The Examiner equates the use in prevention of corneal scar healing with wound healing in general. Although tissue adhesives might be categorized as falling under the general category of "wound healing," compositions used in wound healing are a large genus. Robertson does not teach or suggest using elastase inhibitors for tissue adhesives, and furthermore does not teach or suggest any particular elastase inhibitor, such as eglin or α1-antiprotease, for the purposes of wound healing in general or in combination with fibrin.

Mehta discloses the use of one specific elastase inhibitor, 4-(4-chlorophenyl-sulphonylcarbamoyl)benzoyl-L-valyl-L-proline 1(RS)-(1-trifluoroacetyl-2-methylpropyl)amide, for treating vascular disease. This compound is used to inhibit

neutrophil infiltration and subsequent tissue injury. The Examiner equates the use in inhibiting subsequent tissue injury caused by neutrophil infiltration with wound healing in general. Although tissue adhesives might be categorized as falling under the general category of "wound healing," compositions used in wound healing are a large genus. Mehta does not teach or suggest using elastase inhibitors for tissue adhesives, and furthermore does not teach or suggest any particular elastase inhibitor, such as eglin or α1-antiprotease, for the purposes of wound healing in general.

Atkinson discloses the use of an elastase inhibitor, eglin, in toothpaste, mouthwash, and skin cream compositions for cosmetic and therapeutic purposes. This reference merely indicates the existence of the compound eglin and does not teach or suggest using eglin for wound healing.

Many elastase inhibitors are known in the art, for example, peptide inhibitors (e.g., AAPVCK), chemical compounds (e.g., 4-(4-chlorophenyl-sulphonylcarbamoyl)benzoyl-L-valyl-L-proline 1(RS)-(1-trifluoroacetyl-2-methylpropyl)amide), and enzymes (e.g., eglin, gelin, elafin, α1-antiprotease, elastase α1-antiproteinase inhibitor, leukocyte protease inhibitor). Robertson merely suggests the desirability of using elastase inhibitors in general as epithelial cell health promoters in wound healing. Mehta describes one particular elastase inhibitor, a chemical compound, for treatment of vascular disease. Both references are considered by the Examiner as relevant to the general area of wound healing, but do not relate specifically to fibrinogen tissue adhesives, a specific class of wound healing compositions. Neither reference therefore provides a motivation to use an elastase inhibitor, much less a specific elastase inhibitor such as either eglin or α1-antiprotease, in combination with fibrinogen to make a tissue adhesive. The combination of Hammarstrom or Waldstrom with Robertson or Mehta thus fails to provide a particularized teaching or suggestion to the skilled artisan to make the claimed combination. Atkinson does not cure this defect, as it does not relate to wound healing.

Furthermore, the use of eglin and α1-antiprotease in tissue adhesives is surprisingly effective, as the prior art taught away from the use of elastase inhibitors with tissue adhesive. For fibrinogen-based tissue adhesives, it is desirable to control the durability of the sealant by inhibiting fibrinolysis. Plasmin-mediated fibrinolysis is known, and plasmin inhibitors have been previously used to prevent premature fibrinolysis of a fibrinogen-based tissue adhesive. It had been speculated that besides the plasmin-mediated fibrinolysis, other fibrinolytic processes might exist which are not based on plasmin Simon *et al., Blood* 82(8):2414-2422 (1993)). However, the prior art taught that the non-plasmin fibrinolytic pathway could not be inhibited by a specific elastase-inhibiting peptide (AAPVCK; Simon *et al., Blood* 82(8):2414-2422 (1993)). The present invention demonstrates that elastase inhibitors are surprisingly as effective as the prior art compounds in preventing premature fibrinolysis of fibrinogen-based tissue adhesives via a non-plasmin fibrinolytic pathway.

Example I shows an *in vitro* test for assaying the fibrinolysis-inhibiting action of the elastase inhibitors of the invention. Elastase inhibitors eglin and α1-anti-protease were admixed with a fibrinogen-based tissue adhesive. The ability of these elastase inhibitors to prevent fibrinolysis of the tissue adhesive was compared to that of aprotinin, a plasmin inhibitor. Surprisingly, figures 1 and 2 show that the elastase inhibitors eglin and α1-anti-protease were at least as effective, if not more effective, than the plasmin inhibitor in prevention fibrinolysis of the fibrinogen-based tissue adhesive, as compared to the fibrinogen-based tissue adhesive alone.

Example II shows *in vivo* tests using both hyper-fibrinolytic and normal - fibrinolytic conditions. Fibrinogen-based tissue adhesives containing eglin, an elastase inhibitor, were compared to tissue adhesives alone or those containing aprotinin, a plasmin inhibitor. Surprisingly, figures 3 and 4 show that the elastase inhibitor eglin was at least as effective, if not more effective, than the plasmin inhibitor in preventing fibrinolysis of the fibrinogen-based tissue adhesive, as compared to the fibrinogen-based tissue adhesive alone.

The cited references in combination fail to provide a particularized motivation to combine fibrinogen with either eglin or α1-anti-protease. Hammarstrom and Waldstrom teach fibrin-based tissue adhesives, but do not describe the use of any elastase inhibitors in their compositions, let alone eglin and α1-anti-protease. The secondary references Robertson and Mehta fail to cure this deficiency. Neither Robertson nor Mehta teach or disclose the use of elastase inhibitors eglin or α1-anti-protease for use in wound healing. Therefore, one of skill in the art would not have been motivated to select the combination of fibrinogen and eglin or α1-anti-protease to prepare a tissue adhesive with desired anti-fibrinolysis properties.

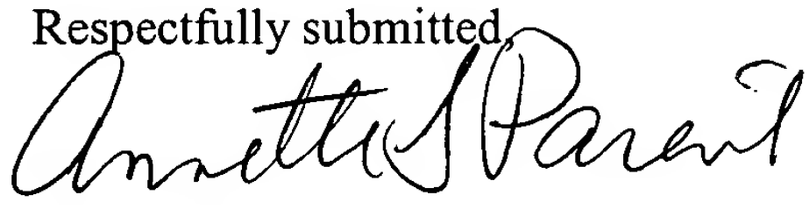
Furthermore, the present invention demonstrates that the elastase inhibitors eglin and α1-anti-protease, when used in combination with a fibrinogen-based tissue adhesive, have the unexpected property of preventing fibrinolysis of the adhesive at least as well as the prior art plasmin compounds. The elastase inhibitors eglin and α1-anti-protease can be used alone or in combination with plasmin inhibitor compounds to prevent premature fibrinolysis of a fibrinogen-based tissue adhesive. Applicants respectfully request the withdrawal of the rejections under 35 USC §103.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (415) 576-0200.

Respectfully submitted,



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